

General

Guideline Title

Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

Bibliographic Source(s)

Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2010 May 4;74(18):1463-70. [40 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003 Nov 25;61(10):1332-8.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2013.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Note from the American Academy of Neurology (AAN) and National Guideline Clearinghouse (NGC): This guideline review contains no new efficacy evidence that would change the recommendation from the previous report, so the 2003 recommendations are included as well as the 2010 conclusions.

2003 Recommendations

1. On the basis of evidence from a single Class I study and a few Class II or III studies, it appears that mitoxantrone may have a beneficial effect on disease progression in patients with multiple sclerosis (MS) whose clinical condition is deteriorating (Type B recommendation). In general, however, this agent is of limited use and of potentially great toxicity. Therefore, it should be reserved for patients with rapidly advancing disease who have failed other therapies.

2. On the basis of several consistent Class II and III studies, mitoxantrone probably reduces the clinical attack rate and reduces attack-related magnetic resonance imaging (MRI) outcomes in patients with relapsing MS (Type B recommendation). The potential toxicity of mitoxantrone, however, considerably limits its use in patients with relapsing forms of MS.
3. Because of the potential toxicity of mitoxantrone, it should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapeutic agents (Type A Recommendation). In addition, patients being treated with mitoxantrone should be monitored routinely for cardiac, liver, and kidney function abnormalities (Type A Recommendation).

2010 Update

Conclusions

While the Class III and IV evidence available provides conflicting estimates of both the frequency and severity of mitoxantrone (MX)-related cardiotoxicity, asymptomatic decreased systolic function occurs in approximately 12% of patients treated with MX, and congestive heart failure (CHF) occurs in approximately 0.4%. The literature on therapy-related acute leukemia (TRAL) in MX-treated patients with multiple sclerosis (MS) is also limited to Class III and IV evidence; however, the cumulative incidence appears to be ~0.8%. Both TRAL and systolic dysfunction can occur at any time after initiation of MX, including early in the treatment course.

The evidence regarding toxicity suggests the risk of systolic dysfunction associated with the use of MX in patients with MS results in a number needed to harm (NNH) of 8, and the risk of TRAL with MX therapy results in an NNH of 123. This demonstrates that the risk of both cardiotoxicity and leukemia is likely higher than earlier estimates.

Clinical Context

Recommendations on MX use reflecting the potential for harm would require a risk-benefit analysis and are beyond the scope of an evidence-based guideline. In the absence of such an analysis, it is reasonable for clinicians to follow the recommendations outlined in the product monograph and include ejection fraction assessments before initiating treatment and administering each dose of MX and yearly after discontinuation of treatment. It is not known whether patients treated with MX with asymptomatic decreased left ventricular ejection fraction (LVEF) will experience long-term sequelae. The long-term sequelae of asymptomatic cardiotoxicity are not clear. It is reasonable for clinicians to monitor patients for TRAL after MX therapy with periodic complete blood cell counts, although the optimal timing of such monitoring is not known.

Clinicians contemplating MX administration for an individual patient with MS must weigh the potential or benefit against the potential for harm given the ~12% risk of systolic dysfunction and ~0.8% risk of TRAL and the availability of alternative therapies with less severe toxicities (e.g., interferon- β and glatiramer acetate) for patients with relapsing-remitting multiple sclerosis [RRMS]).

Definitions:

American Academy of Neurology (AAN) Classification of Evidence for Therapeutic Articles

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.
- e. For non inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome

assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

* Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g, blood tests, administrative outcome data).

AAN Classification of Evidence for Screening Articles

Class I: A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class II: A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class III: A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

Classification of Recommendations

A - Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B - Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C - Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Multiple sclerosis (MS), including:

- Relapsing remitting MS (RRMS)
- Secondary progressive MS (SPMS)
- Progressive-relapsing MS

Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

Clinical Specialty

Neurology

Pharmacology

Intended Users

Physicians

Guideline Objective(s)

To examine the available literature on the efficacy and safety of mitoxantrone use in patients with multiple sclerosis (MS) since the (2003) initial report

Target Population

Patients with multiple sclerosis, including aggressive relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis

Interventions and Practices Considered

Mitoxantrone (Novantrone) for treatment of multiple sclerosis

Major Outcomes Considered

- Disease progression
- Clinical attack rate
- Magnetic resonance imaging (MRI) activity
- Long-term sequelae
- Adverse effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

2010 Guideline

The OVID MEDLINE and the Cochrane Controlled Trials Database were searched using the keywords mitoxantrone (MX) and multiple sclerosis (MS). All articles published in English before July 2009 with both of these terms were retrieved (i.e., only articles pertaining to MX use in MS were considered). Recently published articles were also sought through manual searches of neurology journals and reference lists of relevant publications. Abstracts from the American Academy of Neurology (AAN) annual meetings and the European Committee for Treatment and Research in Multiple Sclerosis Annual Conferences from 2002 to 2009 were also manually reviewed for case reports of leukemia following MX therapy.

For assessment of efficacy, only controlled clinical trials or cohort studies (Class I and Class II evidence for therapeutic articles; see "Rating Scheme for the Strength of Evidence" field) with defined clinical or magnetic resonance imaging (MRI) endpoints published since the first Therapeutics and Technology Assessment (TTA) review were included in the analysis. For assessment of cardiotoxicity and therapy-related acute leukemia (TRAL), all published information, including case series or case reports and abstracts from poster or oral presentations, was reviewed (Class I–Class IV evidence for screening articles; see "Rating Scheme for the Strength of Evidence" field).

2013 Reaffirmation

Medline and Cochrane databases were searched between 2010 May 4 and 2013 July 13 for the terms mitoxantrone and multiple sclerosis. Controlled clinical trials or cohort studies with defined clinical or MRI endpoints published since the previous review were included. For assessment of cardiotoxicity and TRAL, all published information, including case series or case reports and abstracts from poster or oral presentations, was reviewed.

Number of Source Documents

A total of 434 articles and abstracts was retrieved through electronic searches and manual searching of abstracts and recent journal volumes. Seventeen efficacy studies published after the last Therapeutics and Technology Assessment (TTA) report were identified, including 2 Class I or II studies and 15 Class III or IV studies. Only the Class I and II studies were included in our evaluation. Eleven published Class III studies provided sufficient details to assess cardiotoxicity. Treatment-related acute leukemia (TRAL) was reported in 31 studies (including 4 poster/oral presentation abstracts), predominantly in small case series or individual case reports (Class III–IV).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

American Academy of Neurology (AAN) Classification of Evidence for Therapeutic Articles

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

- a. Concealed allocation
- b. Primary outcome(s) clearly defined
- c. Exclusion/inclusion criteria clearly defined
- d. Adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.
- e. For non inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or non-inferiority.
 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective).
 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.

4. The interpretation of the results of the study is based upon a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-e above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**

Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.

* Note that numbers 1-3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

AAN Classification of Evidence for Screening Articles

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Class IV: Studies not meeting Class I, II or III criteria including consensus, expert opinion or a case report.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Relevant articles were obtained through a review of the medical literature and the strength of the available evidence was graded according to the American Academy of Neurology evidence classification scheme. Evidence tables are provided in the original guideline document.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2010 Guideline

Not stated

2013 Reaffirmation

An author conducted a literature search using the same criteria as presented in the original guideline. Because the guideline recommendations would not change given the new literature available, the committee voted to reaffirm the guideline, stating that the conclusions and recommendations are still valid.

Rating Scheme for the Strength of the Recommendations

Classification of Recommendations

A - Established as effective, ineffective, or harmful for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

B - Probably effective, ineffective, or harmful for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

C - Possibly effective, ineffective, or harmful for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Approved by the Therapeutics and Technology Assessment Subcommittee on September 10, 2009; by the Practice Committee on September 22, 2009; and by the American Academy of Neurology (AAN) Board of Directors on December 14, 2009.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of mitoxantrone in the treatment of multiple sclerosis

Potential Harms

The accumulated Class III and IV evidence suggests an increased incidence of systolic dysfunction and therapy-related acute leukemia (TRAL) with mitoxantrone therapy. Systolic dysfunction occurs in ~12% of patients with multiple sclerosis (MS) treated with mitoxantrone, congestive heart failure occurs in ~0.4%, and leukemia occurs in ~0.8%. The number needed to harm is 8 for systolic dysfunction and 123 for TRAL.

Qualifying Statements

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This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Marriott JJ, Miyasaki JM, Gronseth G, O'Connor PW, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2010 May 4;74(18):1463-70. [40 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2003 Nov 25 (revised 2010 May; reaffirmed 2013 Jul 13)

Guideline Developer(s)

American Academy of Neurology - Medical Specialty Society

Source(s) of Funding

American Academy of Neurology (AAN)

Guideline Committee

Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

Composition of Group That Authored the Guideline

Primary Authors: James J. Marriott, MD; Janis M. Miyasaki, MD, MEd, FAAN; Gary Gronseth, MD, FAAN; Paul W. O'Connor, MD, MSc

Therapeutics and Technology Assessment Subcommittee Members: Janis M. Miyasaki, MD, MEd, FAAN (Co-Chair); Cynthia L. Harden, MD (Co-Chair); Richard M. Camicioli, MD; Terry D. Fife, MD, FAAN; Cheryl Jaigobin, MD; Barbara S. Koppel, MD, FAAN; Jason Lazarou, MD; Alexander Rae-Grant, MD; James C. Stevens, MD, FAAN (Ex-Officio); William H. Theodore, MD, FAAN.

Financial Disclosures/Conflicts of Interest

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interests to influence the recommendation of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, Neurology® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com

Dr. Marriott has served on a scientific advisory board for Biogen Idec; has received funding for travel from EMD Serono, Inc. and Biogen Idec; and has received a speaker honorarium from Teva Pharmaceutical Industries Ltd. Dr. Miyasaki has served on a scientific advisory board for Teva Pharmaceutical Industries Ltd.; has received honoraria for educational activities not funded by industry; serves on the editorial board of Movement Disorders; has received speaker honoraria from Biovail Corporation; serves/has served as a consultant to Ortho-McNeil-Janssen Pharmaceuticals, Inc., Merz Pharmaceuticals, LLC, Schering-Plough Corp., the NIH (Independent Medical Monitor), Ontario Drug Benefits, and Common Drug Review, Canada; and receives research support from Teva Pharmaceutical Industries Ltd., Boehringer Ingelheim, Solvay Pharmaceuticals, Inc., Solstice Neurosciences, Inc., Impax Laboratories, Neurogen, Medivation, Inc., the National Parkinson Foundation, the Parkinson Society Canada, the Michael J. Fox Foundation, and the Huntington Study Group. Dr. Gronseth serves as an editorial advisory board member of *Neurology Now*; serves on a speakers' bureau for Boehringer Ingelheim; and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. Dr. O'Connor has served on scientific advisory boards for Novartis, Sanofi-Aventis, Bayer Schering Pharma, Genentech, Inc., and Roche; has received funding for travel from Biogen Idec, Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Biogen Idec; serves as a consultant for Biogen Idec, Bayer Schering Pharma, Daiichi Sankyo, Abbott, Genzyme Corporation, BioMS Medical, Schering-Plough Corp., Novartis, EMD Serono, Inc., Sanofi-Aventis, Teva Pharmaceutical Industries Ltd., and Genentech, Inc.; has received research support from Biogen Idec, Schering-Plough Corp., BioMS Medical, Genentech, Inc., Bayer Schering Pharma, Novartis, Sanofi-Aventis, Roche, and the NIH (1 U01 NS 45719-01 A1 [Site PI]); and estimates that 25% of his clinical effort is spent on evoked potentials in MS diagnosis.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003 Nov 25;61(10):1332-8.

The American Academy of Neurology (AAN) reaffirmed the currency of the guideline in July 2013.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

A list of American Academy of Neurology (AAN) guidelines, along with a link to this guideline, is available at the [AAN Web site](#)

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Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 201 Chicago Avenue South, Minneapolis, MN 55415.

Availability of Companion Documents

The following are available:

- E-Appendices. Evidence report: the efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis. Data supplement [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the [Neurology Journal Web site](#) .
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the [AAN Web site](#) .

Patient Resources

The following is available:

- Multiple sclerosis: safety and effectiveness of mitoxantrone treatment. American Academy of Neurology (AAN). 2010. 2 p. Available from the [AAN Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on August 17, 2004. The information was verified by the guideline developer on September 9, 2004. This summary was updated by ECRI on May 27, 2005, following the U.S. Food and Drug Administration (FDA) advisory on Novantrone (mitoxantrone for injection concentrate). This summary was updated by ECRI Institute on August 11, 2008 following the U.S. Food and Drug Administration advisory on mitoxantrone hydrochloride. This summary was updated by ECRI Institute on February 25, 2011. The currency of the guideline was reaffirmed by the developer in July 2013 and the summary was updated by ECRI Institute on December 22, 2015.

Copyright Statement

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